International Journal of Environmental Sciences
ISSN: 2229-7359
Vol. 10 No. 1s, 2024
https://theaspd.com/index.php

Computational Prediction Of The Pharmacokinetics, Bioactivity And Toxicity Parameters Of The Local Anesthetic Ambucaine

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Abstract:
Computer aided drug design plays an important role in drug discovery and development and has become an essential tool in the pharmaceutical industry. In the present research study, the free online computational program Molinspiration Cheminformatics Toolkit (http://www.molinspiration.com) was used to evaluate the pharmacokinetic properties of ambucaine based on Lipinski's rule of five. Miscreen (http://www.molinspiration.com), a molinspiration virtual screening engine, was used to calculate bioactivity scores for ambucine. This computational tool is used to find ligands that modulate GPCRs, ion channels, nuclear receptors, and to identify kinase inhibitors, protease inhibitors, and enzyme inhibitors.
The molecular properties of ambucaine were calculated using Molinspiration Cheminformatics and the data are shown in the table. Ambucaine drug similarity was evaluated by Lipinski's rule of five, which deals with four simple physicochemical parameters (log P ≤ 5, molecular weight ≤ 500, number of hydrogen bond acceptors ≤ 10, number of hydrogen bond donors ≤ 5). Log P measurements are used to understand the dissolution behavior of a substance and thus its oral absorption and bioavailability. Ambucaine has a log P value of 3.47, indicating that it is highly lipophilic or hydrophobic. Therefore, we identify a better distribution of ambucaine after absorption in the body. The molecular weight of ambucaine was 308.42, which is within the range of ≤500. Compounds with low molecular weight are easily absorbed, distributed and transported compared to compounds with high molecular weight >500. Ambucaine also has an appropriate number of hydrogen bond acceptors and hydrogen bond donors, i.e. 2 and 5, to ensure efficient interaction with the hydrogen bond groups of refractory receptors. 10 number of rotatable bond in ambucaine explains the flexibility and conformational changes of ambucaine upon binding to receptors. It is accepted that the number of rotatable bonds should be 10 or less to confer oral bioavailability. The TPSA value of 64.80 for ambucaine shows a good intestinal absorption and blood-brain barrier penetration rate. In addition, ambucaine does not violate Lipinski's parameters, making it a drug-like molecule.
The Ambucaine has exhibited calculated bioactivity score -0.01 for GPCR ligand, 0.09 for Ion channel modulator, -0.03 for Kinase inhibitor, -0.10 for nuclear receptor ligand, -0.11 for Protease inhibitor, and -0.02 for Enzyme inhibitor.
Keywords: *CADD, Molinspiration, Cheminformatics, Local anaesthetic, Ambucaine*

INTRODUCTION:

The use of scientific and technological innovations as a research tool combining multidisciplinary informatics, biotechnology, chemistry, and biology knowledge is essential for optimizing time and reducing cost in the drug design. Thus, the integration of these *in silico* techniques makes it possible to search for new drugs with better pharmacokinetic and toxicological profiles compared to commercially used drugs.[1] Many computer-based software are available through internet, which helps to understand the molecular properties, bioactivity, and toxicity of generated structures. Hence, the present investigation is aimed to reinvestigate and identify some anti-infective and anticancer agents from local anaesthetics having good pharmacokinetic and safety profile by using computational methods. The main objective of the present study is to determine the *in silico* molecular properties and toxicity profile of Local anaesthetic drug Ambucaine.

MATERIALS AND METHODS:

There are various physicochemical descriptors and pharmacokinetic relevant properties of the anti-arrhythmic agents were evaluated by using the tool Molinspiration Cheminformatics server (http://www.molinspiration.com). Molinspiration Cheminformatics offers broad range of tools supporting molecule manipulation and processing, including SMILES and SDfile conversion, normalization of molecules, generation of tautomers, molecule fragmentation, calculation of various molecular properties

needed in QSAR, molecular modelling and drug design, high quality molecule depiction, molecular database tools supporting substructure and similarity searches. This software also supports fragment-based virtual screening, bioactivity prediction and data visualization. Molinspiration tools are written in Java, therefore can be used practically on any computer platform [4-5]. The Lipinski rule of five deals four simple physicochemical parameters ranges (MWT ≤ 500, log P ≤ 5, Hbond donor's ≤ 5, H-bond acceptors ≤ 10) associated with 90% of orally active drugs that have passed phase II clinical status [6]. There are several scoring methods such as ligand efficiency and lipophilic efficiency can be used to express drug likeness as measure of potency. These physicochemical descriptors are associated with aqueous solubility and intestinal permeability within acceptable range.

RESULTS:

1. Ambucaine Structure

originalSMILES: CCCCOC1=C(C=CC(=C1)N)C(=O)OCCN(CC)CC
miSMILES: CCCCOC1=C(C=CC(=C1)N)C(=O)OCCN(CC)CC

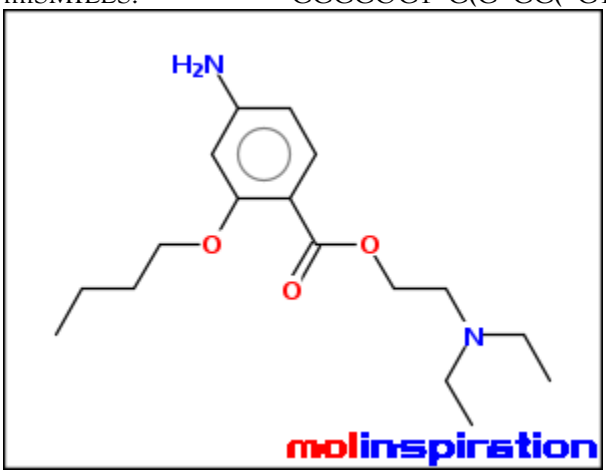

Fig. 1: Ambucaine Structure

2. **Molecular Properties:** Molinspiration property engine v2021.10

Table No. 1: Molecular properties of Ambucaine

Sr. No	Molecular Descriptor	Obsrved Values
1	miLogP	3.47
2	TPSA	64.80
3	natoms	22
4	MW	308.42
5	nON	5
6	nOHNH	2
7	nviolations	0
8	nrotb	10
9	volume	312.37

3. **Bioactivity Score:** Molinspiration bioactivity score v2021.03

Table No. 2: Bioactivity score of Ambucaine

Sr. No.	Bioactivity	Score
1	GPCR ligand	0.01
2	Ion channel modulator	-0.09
3	Kinase inhibitor	-0.03
4	Nuclear receptor ligand	-0.10
5	Protease inhibitor	-0.11

6	Enzyme inhibitor	-0.02

DISCUSSION:

The molecular properties of ambucaine were calculated using Molinspiration Cheminformatics and the data are shown in the above table. Ambucaine drug similarity was evaluated by Lipinski's rule of five, which deals with four simple physicochemical parameters (log P ≤ 5, molecular weight ≤ 500, number of hydrogen bond acceptors ≤ 10, number of hydrogen bond donors ≤ 5). Log P measurements are used to understand the dissolution behavior of a substance and thus its oral absorption and bioavailability. Ambucaine has a log P value of 3.47, indicating that it is highly lipophilic or hydrophobic. Therefore, we identify a better distribution of ambucaine after absorption in the body. The molecular weight of ambucaine was found to be 308.42, which is within the range of ≤500. Compounds with low molecular weight are easily absorbed, distributed and transported compared to compounds with high molecular weight >500. Ambucaine also has an appropriate number of hydrogen bond acceptors and hydrogen bond donors, i.e. 2 and 5, to ensure efficient interaction with the hydrogen bond groups of refractory receptors. 10 number of rotatable bond in ambucaine explains the flexibility and conformational changes of ambucaine upon binding to receptors. It is accepted that the number of rotatable bonds should be 10 or less to confer oral bioavailability. The TPSA value of 64.80 for ambucaine shows a good intestinal absorption and blood-brain barrier penetration rate. In addition, ambucaine does not violate Lipinski's parameters, making it a drug-like molecule.

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CONCLUSION:

All molecular properties of ambucaine are found to be within acceptable range and showed good pharmacokinetic properties. Ambucaine shows zero voilations towards Lipinski rule of five which makes it more promising drug like molecule. Ambucaine has exhibited better biological activity as tyrosine kinase inhibitor and showed better bioactivity score for nuclear receptor ligand.

Conflict of interest:

The authors declare that there is no conflict of interest regarding the publication of this research manuscript.

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